Role of advanced neuroimaging, fluid biomarkers and genetic testing in the assessment of sport-related concussion: a systematic review

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ABSTRACT

Objective To conduct a systematic review of published literature on advanced neuroimaging, fluid biomarkers and genetic testing in the assessment of sport-related concussion (SRC).

Data sources Computerised searches of Medline, PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, Scopus and Cochrane Library from 1 January 2000 to 31 December 2016 were done. There were 3222 articles identified.

Study selection In addition to medical subject heading terms, a study was included if (1) published in English, (2) represented original research, (3) involved human research, (4) pertained to SRC and (5) involved data from neuroimaging, fluid biomarkers or genetic testing collected within 6 months of injury. Ninety-eight studies qualified for review (76 neuroimaging, 16 biomarkers and 6 genetic testing).

Data extraction Separate reviews were conducted for neuroimaging, biomarkers and genetic testing. A standardised data extraction tool was used to document study design, population, tests employed and key findings. Reviewers used a modified quality assessment of studies of diagnostic accuracy studies (QUADAS-2) tool to rate the risk of bias, and a modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to rate the overall level of evidence for each search.

Data synthesis Results from the three respective reviews are compiled in separate tables and an interpretive summary of the findings is provided.

Conclusions Advanced neuroimaging, fluid biomarkers and genetic testing are important research tools, but require further validation to determine their ultimate clinical utility in the evaluation of SRC. Future research efforts should address current gaps that limit clinical translation. Ultimately, research on neurobiological and genetic aspects of SRC is predicted to have major translational significance to evidence-based approaches to clinical management of SRC, much like applied clinical research has had over the past 20 years.

INTRODUCTION

Over the past decade, there has been major progress in the methods for evaluation of sport-related concussion (SRC) and in determining the natural history of *clinical* recovery after injury.[1–4] Critical questions remain, however, about the acute *neurobiological* effects of SRC on brain structure and function, and the eventual time course of *physiological recovery* after injury.

Studies using advanced neuroimaging techniques have demonstrated that concussion is associated with metabolic and physiological changes in the brain, which correlate with postconcussive symptoms and performance on neurocognitive testing during the acute postinjury phase.[5–12] In parallel, the assessment of novel and selective blood biomarkers and genetic testing for traumatic brain injury (TBI) has rapidly expanded, but with limited application to the study of SRC. Extending from the broader TBI literature, there is also increasing interest in the role of genetics in predicting risk of injury, prolonged recovery and long-term neurological health problems associated with SRC and repetitive head impact exposure in athletes.[13]

Clinically, there is a need for diagnostic biomarkers as a more objective means to assess the presence/severity of concussion in athletes. Beyond the potential diagnostic utility, there is also keen interest in the development of prognostic biomarkers of recovery after SRC. Emerging data suggest that physiological abnormalities may persist beyond the typical window of clinical recovery after mild traumatic brain injury (mTBI), which raises concerns about risks associated with repeat injury during the acute recovery phase.[14 15] Most concerning is that a *window of cerebral vulnerability* may extend beyond the point of clinical recovery, when the brain remains physiologically compromised and athletes are at heightened risk of repetitive injury. Imaging and blood biomarkers that reliably reflect the extent of neuronal, axonal and glial damage and/or microscopic pathology could conceivably diagnose and predict clinical recovery outcome after SRC.

We conducted a systematic review of the existing literature on the utility of advanced imaging, fluid biomarkers and genetic testing in the assessment of SRC.

METHODS

Systematic review methodology[16] was employed to address the following core questions for the 5th International Consensus Conference on Concussion in Sport:

- *What advanced or novel tests can assist in the assessment of SRC?*
- *What is the role for advanced neuroimaging?*
- *What is the role for cerebral spinal fluid (CSF), blood, and urine and saliva biomarkers?*

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Table 1 Medical subject heading terms and key words used for electronic database searches

	(Concussion OR concuss* OR brain injuries OR head injuries OR ((head OR brain) AND injur*) OR Post-Concussion Syndrome OR postconcussion* OR Mild traumatic brain injury OR MTBI OR acquired brain injury OR blunt head trauma OR Craniocerebral Trauma OR (('mild traumatic' OR acquired) AND brain injur*)) AND (athletes OR sports OR sport OR sporting OR athleti* OR athlete* OR recreation OR recreat* OR baseball OR bicycling OR boxing OR cycling OR diving OR equestrian OR equine OR football OR Head Protective Devices OR helmet* OR hockey OR lacrosse OR martial arts OR karate OR judo OR tae kwon do OR aikido OR mountaineering OR racquet sports OR rugby OR skating OR skiing OR snow sports OR soccer OR wrestling)		
Head injury and relevant sports.	**Neuroimaging search**	**Biomarkers search**	**Genetics search**
Advanced or novel tests	(Neuroimaging OR radiological OR neuroradiological OR brain imaging OR Positron-Emission Tomography OR ((PET OR MRI) AND (scan OR scans)) OR Magnetic Resonance Imaging OR ((structural OR Functional) AND MRI) OR spectroscopy OR Magnetic Resonance Spectroscopy OR Diffusion Tensor Imaging OR Arterial Spin Labeling OR Electroencephalography OR EEG OR Diagnostic Techniques, Neurological OR Magnetoencephalography OR Fluid-attenuated inversion recovery OR Diagnostic imaging OR Quantitative EEG OR QEEG OR event-related potentials OR 'event related potential*' OR 'evoked potential*' OR ERP OR scanning OR fMRI OR 'resting-state' OR 'resting state')	(Biomarkers OR biomarker OR neuroendocrine OR pituitary OR hormone* OR cortisol OR hydrocortisone OR gonadal steroid hormones OR growth hormone OR thyroid OR SIADH OR Inappropriate ADH Syndrome OR ((Cerebrospinal OR 'cerebro spinal') AND fluid*) OR CSF OR Serum OR urine OR saliva OR neuronal OR glial OR neuroglia OR axonal OR (Marker* AND (immunologic OR laboratory OR clinical OR biochemical OR immune OR immunologic OR biological OR biologic)))	(Epigenetic* OR Epigenomics OR 'copy number' OR 'rare variant*' OR Genetic Variation OR 'genetic diversit*' OR genotype OR genogroup* OR genotype* OR genetics OR genetic* OR mitochondria OR mitochond* OR Intracellular signaling peptides and proteins OR Polymorphism, Genetic OR DNA Copy Number Variations OR 'DNA polymorphism' OR 'genotype environment interaction' OR Polymorphism, Single Nucleotide OR 'Intracellular signaling' OR genome OR OR genomics OR genom* OR allele OR allel* OR chromosomes OR chromosom* OR 'genetic testing')

► *What is the role for genetic or epigenetic testing?*

Three separate systematic literature searches (neuroimaging, biomarkers and genetics) were conducted to address each of the outlined questions above. The stepwise approach and workflow for our systematic searches were registered with an international prospective register of systematic reviews[17] (see online supplementary appendices 1–3). Prior reviews have separately evaluated the state of the science on imaging, biomarkers and genetics in the broader spectrum of TBI or SRC,[18–22] but this is the first integrated review of the most up-to-date evidence on these novel technologies specific to SRC.

Databases and search terms

Our literature search used PubMed/Medline, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and Cochrane Library. Given the focus of this systematic review on the evolution of emerging technologies, our search was limited to the published literature from 1 January 2000 to 31 December 2016. The decision to include published literature dating back to 2000 was based on the relevance of modern technologies to our specific review question; this approach is further supported by the finding that the earliest publication of articles meeting our inclusion criteria was 2004 for MRI, 2013 for biomarkers and 2015 for genetics. The search strategy was developed in conjunction with an expert medical librarian, who also conducted an independent peer review of the strategy. Table 1 summarises the combination of key words and medical subject headings (MeSH) terms used for the three respective searches. A common group of search terms for head injury and sport was used for all three searches, then combined with the specific terms for searches related to neuroimaging, biomarkers and genetics.

Study selection criteria

In addition to meeting the MeSH term criteria, the basic requirements for a study to be included in our search were that the article (1) was published in English, (2) represented original research, (3) involved human research, (4) pertained only to SRC (ie, not non-sports TBI), (5) included data from studies involving neuroimaging (including electrophysiological testing), fluid biomarkers or genetic testing in the assessment of SRC, and (6) had at least one data collection point within 6 months of injury. Two reviewers collaboratively screened articles for inclusion. Titles and abstracts were reviewed first, and duplicates and irrelevant articles were excluded, followed by full-text screenings. A third reviewer was consulted to resolve discrepancies about article inclusion.

Data extraction and analysis

Members of the author group extracted relevant data from included studies to populate the data extraction tool for each search. The author group then conducted reviews relevant to each search based on their respective area of subject matter expertise (neuroimaging, biomarkers and genetics). For the included studies, a standardised data extraction method was used (see tables 2–4 for the data extraction tools for the neuroimaging, biomarker and genetic searches). Articles are listed in chronological order based on publication year to illustrate the pattern and evolution of research over time. Two subject matter experts from our working group independently examined all retrieved citations to determine eligibility for inclusion.

Assessment of risk of bias and level of evidence

As recommended by the Cochrane Collaboration, a modified version of the QUADAS-2 was used to assess the risk of bias for identified diagnostic accuracy studies[23] (see online supplementary appendix 1). Generalisability was assessed based on the degree of representativeness across age, gender and sport. Two primary reviewers for each study independently assessed the risk of bias in identified studies. Using the modified QUADAS-2 tool, the overall risk of bias was assessed (low, moderate and high) for each included study. Discrepancies were resolved by consensus after consulting with an independent third rater.

Table 2 Data extraction tool for studies using neuroimaging

	Study design		Participants					Review of evidence
First author, year	Study type	Modality	Sport	Age/level (mean ± SD, range)	Gender (M/F)	n (control description)	Time from injury to examination	Risk of bias
Chen JK, 2004[11]	PCS	T-fMRI	WR, IH, OT	Control: 27.6±5.2 years; concussed: 26.9±7.2 years	M	16 C+, 8 C– (age-matched males)	1–14 months (mean 4.7 months)	High
Jantzen KJ, 2004[6]	PCS	T-fMRI	FB	20 years; 19–23 years	M	4 C+, 4 C–	Three athletes examined within 1 week postinjury, 1 at end of season	Moderate
Cimatti M, 2006[26]	CS	MRS	BX, OT	UNK	UNK	6 C+	24–48 hours postinjury	High
Gosselin N, 2006[91]	PCS	EEG	IH, FB SCR	Asymptomatic: 26.1±6.1 years; symptomatic: 25.7±7.0 years; control: 22.0±1.8 years	M/F	20 C+, 10 C–	Asymptomatic 5.3±3.1 weeks; symptomatic 15.1±16.6 weeks postinjury	Moderate
Chen JK, 2007[49]	PCS	T-fMRI	Any	Low PCS: 26.9±5.6 years; moderate PCS: 30.8±5.8 years; control: 21.9±1.6 years	M	18 C+, 10 C–	5±6.4 months postinjury	High
Lovell MR, 2007[5]	PCS	T-fMRI	Any	16.6±2.4; 13–24 years	M/F	28 C+, 13 C– (age-matched athletes)	6.6±4.7 days and 33.3±33.8 days postinjury	Moderate
Chen JK, 2008[50]	PCS	T-fMRI	Any	Control: 20±1.2 years; C+ no depression: 26±5.6 years; C+ mild depression: 29±6.7 years; C+ moderate depression: 30±7.4 years	M	40 C+, 16 C– (IH and FB controls)	4.9–7.3 months depending on group	Moderate
Vagnozzi R, 2008[32]	PCS	MRS	RB, BX, OT	27±4.8 years, 21–35 years	M/F	14 C+, 5 C– (age-matched controls)	3, 15 and 30 days postinjury	Moderate
Slobounov S, 2009[63]	PCS	EEG	RB, FB, IH, SCR	Male: 21.3 years; female: 20.8 years; 18–25 years	M/F	21 C+	7, 14 and 21 days postinjury	Moderate
Cao C, 2010[61]	PCS	EEG	RB, FB, IH	Male: 20.9 years; female: 21.4 years; 18–25 years	M/F	29 C+	BL, and 7 days postinjury	Moderate
Henry LC, 2010[27]	PCS	MRS	Any	Control: 23±0.71 years; concussed: 22.1±0.77 years	M	12 C+, 12 C-	Within 6 days postinjury (81.9±46.7 hours)	Moderate
Livingston SC, 2010[92]	PCS	TMS	Any	20.4±1.3 years	M/F	9 C+, 9 C– (age, gender, sport, position, concussion history and LD/ADHD matched)	1, 3, 5 and 10 days postinjury	Moderate
McCrea M, 2010[4]	PCS	qEEG	FB	Col/HS	M	28 C+, 28 C– (age, years of education, GPA and BL performance matched)	BL, day of injury, 8 days and 45 days postinjury	Moderate
Pardini JE, 2010[93]	PCS	T-fMRI	Any	16.3 years, 14–23 years	M/F	16 C+	3–12 days postinjury; median: 6.5 days postinjury	Moderate
Slobounov SM, 2010[53]	PCS	T-fMRI	RB, IH, SCR	Control: 21.3 years; concussed: 20.8 years	M/F	15 C+, 15 C– (age-matched athlete controls)	≤30 days postinjury	Moderate
Vagnozzi R, 2010[30]	PCS	MRS	RB, SCR, BX, OT	Control: 27.6±3.6 years; concussed: 26.5±5.5 years; 16–35 years	M/F	40 C+, 30 C–	3, 15, 22 and 30 days postinjury	Moderate
Zhang K, 2010[48]	PCS	T-fMRI/DTI	RB, IH, SCR	Control: 21.3±1.5 years; concussed: 20.8±1.7 years	M/F	15 C+, 15 C– (age-matched athlete controls)	30±2 days postinjury	Moderate
Cao C, 2011[62]	PCS	EEG	RB, FB, IH, SCR	Male: 21.3 years; female: 20.8 years; range: 18–25 years	M/F	30 C+, 30 C– (age and sex matched athletes from same group without history of concussion)	BL, 30±3 days postinjury	Moderate
Cubon VA, 2011[10]	PCS	DTI	Any	Control: 20.4±1.8 years; concussed: 19.7±1.6 years	M/F	10 C+, 10 C– (sex and age matched non-contact controls)	At least 1 month postinjury mean: 115±104 days	Moderate
Henry LC, 2011[40]	PCS	DTI	FB	Control: 22.8±1.5 years; concussed: 22.1±1.7 years	M	16 C+, 8 C– (FB controls without concussion history)	5 days (mean: 81.9±46.7 hours) and 6 months (mean: 6.4±0.4 months) postinjury	Moderate
Henry LC, 2011[33]	PCS	MRS	FB	22.5 years	M	10 C+, 10 C– (athlete controls without concussion history)	5 days (mean: 81.9±46.7 hours) and 6 months (mean: 6.4±0.4 months) postinjury	Moderate
Len TK, 2011[68]	PCS	CVR	IH, OT	21.4±1.7 years, 16–25 years	M/F	10 C+, 21 C–	4.5±1.1 days postinjury	Moderate
Slobounov SM, 2011[60]	PCS	R-fMRI	RB, IH, SCR	Control: 21.3±1.5 years; concussed: 20.8±1.7 years	M/F	17 C+, 17 C–	10±2 days postinjury	Moderate
Slobounov S, 2011[94]	PCS	EEG	RB, FB, IH, LX, OT	Control: 21.3±1.5 years; concussed: 20.8±1.7 years	M/F	14 C+, 15 C– (student-athletes without history of concussion)	15 days postinjury and within 24 hours of symptom resolution	Moderate

Continued

Table 2 Continued

	Study design		Participants					Review of evidence
First author, year	Study type	Modality	Sport	Age/level (mean ± SD, range)	Gender (M/F)	n (control description)	Time from injury to examination	Risk of bias
Baillargeon A, 2012[95]	PCS	EEG	SCR, IH, RB, FB	Control: 9–12 years (11±1.2 years), 13–16 years (14.8±1.1 years), adults (23.3±3.3 years); concussed 9–12 years (10.5.±1.2 years), 13–16 years (14.2±1.0 years), adults (23.4±2.1 years)	M	48 C+, 48 C–	6 months postinjury	Moderate
Barr WB, 2012[96]	PCS	EEG	FB	Col/HS	M	59 C+, 31 C– (age, years of education, GPA and BL performance matched)	Day of injury, 8 days and 45 days postinjury	Moderate
Breedlove EL, 2012[97]	PCS	T-fMRI	FB	Season 1: 17.0 years, 15–18 years; Season 2: 16.8 years, 14–18 years	M	7 C+	Preseason and in-season follow-up for concussed athletes	High
Chamard E, 2012[36]	PCS	MRS	IH	20.21 years, 18–37.2 years	M/F	45 C+	72 hours, 14 days and 2 months postinjury	Moderate
Johnson B, 2012[28]	PCS	MRS	Any	Control: 20.2±0.8 years; concussed: 20.3±1.5 years	M/F	28 C+, 20 C– (athlete controls)	≤24 hours of symptom resolution, placed into three groups; subjects recovered within 1 week, 2 weeks or 3+ weeks postinjury	Moderate
Johnson B, 2012[56]	PCS	R-fMRI	Any	Control: 20.4±0.8 years; concussed 20.6±1.2 years; additional concussed: 19.9±1.5 years	M/F	23 C+, 15 C– (athlete controls)	14 scanned within 24 hours of symptom resolution (10±2 days postinjury); 9 scanned outside of 24 hours of symptom resolution (10±4 days postinjury)	Moderate
Johnson B, 2012[29]	PCS	MRS	Any	Control: 20.4±0.8 years; concussed: 20.6±1.2 years	M/F	15 C+, 15 C– (athlete controls)	≤24 hours of symptom resolution	Moderate
Livingston SC, 2012[98]	PCS	TMS	Any	20.4±1.3 years	M/F	9 C+, 9 C– (age, gender, sport, position, concussion history and LD/ADHD matched)	1, 3, 5 and 10 days postinjury	Moderate
Maugans TA, 2012[37]	PCS	DTI, MRS, ASL	FB, SCR, WR	11–15 years	M/F	12 C+, 12 C– (age and gender matched)	≤72 hours, 14 days and 30 days postinjury	Moderate
McAllister TW, 2012[99]	PCS	DTI	FB, IH	Col/HS	M	10 C+	Preseason, ≤10 days of injury	Moderate
Slobounov S, 2012[64]	PCS	EEG	RB, FB, IH, SCR	Male: 21.8 years; female: 20.1 years; 18–25 years	M/F	49 C+, 383 C– (athletes evaluated at BL)	BL, 7 days, 15 days, 30 days, 6 months and 12 months postinjury	Moderate
Zhang K, 2012[100]	PCS	R-fMRI	RB, FB, IH, SCR	Control: 20.9±1.1 years; concussed: 20.8±1.5 years	M/F	14 C+, 17 C–	≤24 hours of symptom resolution 10±2 days postinjury	Moderate
Borich M, 2013[38]	PCS	DTI	IH	Control: 15.7±0.9; concussed: 15.5±1.2 years	M/F	12 C+, 10 C– (age, gender and physical activity matched controls)	35.6±15.0 days postinjury	High
Hammeke TA, 2013[101]	PCS	T-fMRI	FB	Control: 16.5±0.52 years; concussed: 16.5±0.52 years	M	12 C+, 12 C– (uninjured teammate; age, education and preseason symptom matched)	13 hours and 7 weeks postinjury	Moderate
Len TK, 2013[67]	PCS	CVR	IH, OT	19.7±3.3 years	M/F	20 C+	BL, 2, 4 and 7 days postinjury, and end of season	Moderate
Prichep LS, 2013[65]	PCS	EEG	FB	17.9 years, 15.1–23.2 years	M	65 C+	≤24 hours, 8 and 45 days postinjury	Moderate
Vagnozzi R, 2013[31]	PCS	MRS	Any	Control: 25.9±5.7 years; concussed: 24.6±6.4 years; 16–35 years	M/F	11 C+, 11 C– (sex and age matched)	3, 15, 30 and 45 days postinjury	Moderate
Virji-Babul N, 2013[44]	PCS	DTI	IH, RB, OT	14–17 years	M/F	12 C+, 10 C-	≤2 months postinjury	High
Bartnik-Olson BL, 2014[25]	PCS	ASL, DTI, MRS	FB, OT	8–17 years	M/F	15 C+, 15 C– (age, gender and BMI matched controls)	Mean: 5.8±4.8 months postinjury	Moderate
Chamard E, 2014[35]	PCS	MRS	Any	Control: 21.1 years; concussed: 21.4 years	F	11 C+, 10 C– (athletes without history of concussion)	9.4±4.3 days and 181.9±14.6 days postinjury	Moderate

Continued

Table 2 Continued

	Study design		Participants					Review of evidence
First author, year	Study type	Modality	Sport	Age/level (mean ± SD, range)	Gender (M/F)	n (control description)	Time from injury to examination	Risk of bias
Dettwiler A, 2014[47]	PCS	T-fMRI	Any	19.8±0.9 years	M/F	15 C+, 15 C– (age and sex matched normal controls)	≤2 days, 2 weeks and 2 months postinjury	Moderate
Helmer KG, 2014[102]	PCS	SWI	IH	Male: 23±2 years; female: 21±4 years	M/F	11 C+, 45 C– includes same subjects at BL	BL, 72 hours, 2 weeks, 2 months, and end of season	High
Keightley ML, 2014[51]	PCS	T-fMRI	Any	Control: 14±2.3 years; concussed: 14.5±2.3 years	M/F	15 C+, 15 C– (age-matched controls)	Range of 9–90 days postinjury	Moderate
Kontos AP, 2014[104]	PCS	fNIRS	Any	Control: 22±0.3 years; concussed: 22.7±1.3 years	M/F	9 C+, 5 C– (age-matched healthy controls)	Range of 15–45 days postinjury, while still symptomatic	High
Murugavel M, 2014[45]	PCS	DTI	Any	Control: 19.9±1.7 years; concussed: 20.2±1.0 years; 18–22 years	M	21 C+, 16 C– (age and sex matched healthy non-contact controls)	2 days, 2 weeks and 2 months postinjury	Moderate
Pasternak O, 2014[42]	PCS	DTI	IH	17–26 years	M/F	11 C+ (7 with usable postinjury scan)	BL, 72 hours postinjury	Moderate
Powers KC, 2014[105]	PCS	TMS	FB	Control: 20.3±1.5 years; concussed: 20.2±1.2 years	M	8 C+, 8 C– (age and position matched with healthy teammate controls)	1–4 weeks postinjury (on symptom resolution)	Moderate
Sasaki T, 2014[43]	PCS	DTI	IH	Control: 21.3±1.8 years; concussed: 21.7±1.5 years	M/F	16 C+, 18 C– (teammates)	Preseason and postseason, mean time to scan: 95±45 days (range: 42–161 days)	Moderate
Sinopoli KJ, 2014[52]	PCS	T-fMRI	IH, OT	Control: 12.6±1.6 years; concussed: 12.6±1.6 years; 9–15 years	M	13 C+, 14 C–	3–6 months postinjury	Moderate
Teel EF, 2014[106, 107]	PCS	EEG	Any	Control: 21±1 years; concussed: 21±1 years	M/F	7 C+, 12 C–	≤8 days (mean: 5±1)	Moderate
Virji-Babul N, 2014[107]	PCS	EEG	IH, SCR	Control: 15.8±1.3 years; concussed: 16±0.9 years	M	9 C+, 33 C– (soccer player controls)	≤3 months postinjury	High
Balkan O, 2015[108]	PCS	EEG	Any	Control: 16 years; concussed: 16.5 years	M	21 C+, 33 C– (soccer players)	≤3 months postinjury	Moderate
Borich M, 2015[55]	PCS	R-fMRI	IH	Control: 15.7±0.9 years; concussed: 15.5±1.2 years	M/F	12 C+, 10 C– (age, gender and physical activity matched controls)	35.7±15 days postinjury	High
Czerniak SM, 2015[58]	PCS	R-fMRI	Any	Control: 20±0.4 years; concussed: 20.3±0.4 years; 18–22 years	M/F	9 C+, 12 C–	≤6 months postinjury (mean: 112±22 days postinjury)	Moderate
Gay M, 2015[109]	PCS	EEG	Any	Col	UNK	9 C+, 9 C– (age-matched student athletes)	During return-to-play protocol	High
Jing M, 2015[103]		DTI	FB	19–23 years (median: 20 years)	M	3 C+, 8 C-	Within 24 hours postinjury	High
Johnson B, 2015[54]	PCS	T-fMRI	Any	20–22 years	M/F	9 C+, 9 C– (age and sex matched normal volunteers)	Within 7 days postinjury	Moderate
Meier TB, 2015[66]	PCS	ASL	FB	Control: 20.7±1.4 years; concussed: 20.6±1.2 years	M	17 C+, 27 C– (healthy football players)	1 day, 1 week and 1 month postinjury	Moderate
Sikoglu EM, 2015[34]	PCS	MRS	Any	Control: 20.2±0.4 years; concussed: 20.1±0.3 years; 18–22 years	M/F	14 C+, 13 C–	76.45±19.3 (mean ± SE) days postinjury (6–185 days)	Moderate
Yuan W, 2015[110]	PCS	DTI	Any (17/23 sports injury)	11–16.7 years	M/F	23 C+, 20 C– (orthopaedically injured controls)	≤96 hours postinjury	Moderate
Zhu DC, 2015[46]	PCS	R-fMRI, DTI	FB	Control: 20.5±1.8 years; concussed: 20±1.3 years	M	8 C+, 11 C– (college students of comparable age and physical activity)	1, 7 and 30 days postinjury	Moderate
Broglio SP, 2016[111 112]	PCS	EEG	Any	Control: 17.1±2.9 years; concussed: 16.3±2.2 years	M/F	24 C+, 21 C–	While symptomatic, at time of self-reported symptom resolution, at return to play and at 1 month postasymptomatic	Moderate

Continued

Table 2 Continued

	Study design		Participants					Review of evidence
First author, year	Study type	Modality	Sport	Age/level (mean ± SD, range)	Gender (M/F)	n (control description)	Time from injury to examination	Risk of bias
Chamard E, 2016[39]	PCS	DTI	IH, SCR, OT	Control: 21±1.4 years; concussed: 21.4±1.7 years	F	10 C+, 8 C– (female athletes without history of concussion)	6 months postinjury	High
Jarrett M, 2016[112]	PCS	SWI	IH	Control: 22.9±2.3 years; concussed: 21.2±3.1 years	M/F	11 C+, 15 C– (college students)	72 hours, 2 weeks and 2 months postinjury	Moderate
Kontos AP, 2016[113]	PCS	EEG	Any	Control: 18.3±2.2 years; PTM: 16.5±1.5 years; NO-PTM 16.5±2.3 years; 18–22 years	M/F	15 PTM, 22 NO-PTM, 20 C– (healthyhealthy age, sex, and concussion history matched)	1, 2, 3 and 4 weeks postinjury	Moderate
Lancaster MA, 2016[15]	PCS	DTI	FB	Control: 18.0±1.5 years; concussed: 17.6±1.5 years	M	27 C+, 26 C– (age, sex and sport matched controls)	24 hours and 8 days postinjury	Moderate
Meier TB, 2016[59]	PCS	R-fMRI	FB, SCR, OT	Control: 20.3±1.4 years; concussed: 20.3±1.3 years	M/F	43 C+, 51 C– (healthy contact-sport athletes)	24 hours, 1 week and 1months postinjury	Moderate
Meier TB, 2016[41]	PCS	DTI	FB, SCR, OT	Control: 20.3±1.5 years; concussed: 20.1±1.4 years	M/F	40 C+, 46 C– (healthy contact-sport athletes)	24 hours, 1 week and 1 months postinjury	Moderate
Militana AR, 2016[57]	PCS	ASL, T-fMRI, R-fMRI, CVR	SCR, OT	Control: 20±1.6 years; concussed: 19.7±1.2 years	M/F	7 C+, 11 C– (healthy controls without history of concussion	3–6 days postinjury	Moderate
Mutch AC, 2016[69]	PCS	CVR	SCR, IH, FB, OT	Control: 18.5 years; concussed: 15.7 years	M/F	6 C+, 24 C– (normal control atlas)	Between 7 and 279 days postinjury	Moderate
Wang Y, 2016[14]	PCS	ASL	FB	Control: 18±1.76 years; concussed: 17.7±1.5 years	M	18 C+, 19 C– (age, gender, sport and academic achievement matched controls)	24 hours and 8 days postinjury	Moderate
Wright AD, 2016[114]	PCS	DTI	IH	21.2±3.1 years	M/F	11 C+, 34 C–	72 hours, 2 weeks and 2 months postinjury	Moderate

Definitions and coding table 3.
Author indicates last name of first author. Year refers to year of publication. Study type coded as follows: CS, clinical series; PCS, prospective cohort study.
Modality refers to specific form(s) of neuroimaging used in the study: ASL, arterial spin labelling; CVR, cerebrovascular reactivity; DTI/DKI, diffusion tensor/kurtosis imaging; MRS, magnetic resonance spectroscopy; R-fMRI, resting-state functional MRI; T-fMRI, task-related functional MRI; SWI, susceptibility weighted imaging.
Electrophysiological testing: EEG, electroencephalogram;qEEG, quantitative electroencephalogram; ERP, event-related potential; TMS, transcranial magnetic stimulation.
Other: fNIRS, functional near-infrared spectroscopy; SPECT, single photon emission computed tomography.
Sports coded as follows: BX, boxing; FB, football; FH, field hockey; IH, ice hockey; LX, LaCrosse; OT, other; RB, rugby; SCR, soccer; WR, wrestling.
Age/Level coded as follows: Col, college; HS, high school; P, professional; O, other; Y, youth.F/M indicates gender: F, female; M, male; list both if it applies.
Misc: BL, baseline; LD, learning disability; ADHD attention-deficit/hyperactivity disorder; GPA, grade point average; BMI, body mass index; PTM/NO-PTM, post-traumatic migrain. Risk of bias: overall risk of bias rated as low, moderate, high or unclear, based on modified QUADAS-2 critical appraisal tool (see online supplementary appendix 2).

Table 3 Data extraction tool for studies using fluid biomarkers

	Study design		Participants					Review of evidence
First author, year	Study type	Modality	Sport	Age/level (mean ± SD, range)	Gender (M/F)	n (control description)	Time from injury to examination	Risk of bias
Dambinova SA, 2013[70]	PCS	AMPAR	RB, SCR, LX, OT	Control: 21.0±3.3 years; concussed: 21.0±3.0 years	M/F	33 C+, 91 C–	BL and two follow-up time points within 6 months	High
Kiechle K, 2014[71]	PCS	S100B	FB, SCR, OT	25.4±5.5 years	M/F	17 C+, 46 C– (at BL)	BL, ≤3 hours, 2 days, 3 days and 7 days postinjury	Moderate
Shahim P, 2014[72]	PCS	S100B, tau, NSE	IH	28 years, 19–38 years	M	28 C+, 47 C– at BL (preseason)	BL, 1 hour, 12 hours, 36 hours, 144 hours postinjury, and day of return to play	Moderate
Oliver J, 2015[75]	PCS	MBG	FB	Col	M	6 C+, 110 C– at BL (preseason)	BL, 24 hours, 48 hours, 72 hours, 96 hours and 2 weeks postinjury	High
Pham N, 2015[76]	PCS	PrPC, GFAP	IH, FB, SCR, WR, OT	21.2±2.9 years, 18–30 years	M/F	6 C+, 27 C– non-athletes, 76 C– athletes at BL	BL and 1–7 days postinjury	Moderate
Schulte S, 2015[77]	PCS	S100B, NSE	FB	21 years, 18–26 years	M	11 C+	BL, 1 day, return-to-play, end-of-play	High
Shahim P, 2015[74]	PCS	VILIP-1, tau, S100B, NSE	IH	Preseason: 27.6 years; concussed: 27.2 years	M	28 C+, 45 C– at BL (preseason)	BL, 1 hour, 12 hours, 36 hours, 144 hours postinjury, and day of return to play	Moderate
Siman R, 2015[78]	PCS	SNTF	IH	Preseason: 27.6 years; concussed: 27.2 years	M	28 C+, 45 C– at BL (preseason)	BL, 1 hour, 12 hours, 36 hours, 144 hours postinjury, and day of return to play	Moderate
Singh R, 2016[83]	PCS	QUIN, 3HK, KYNA	FB	Control: 20.4±1.5 years; concussed: 20.3±1.1 years	M	18 C+, 18 C– (FB teammates)	1 day, 1 week and 1 month postinjury	Moderate
Bouvier D, 2016[73]	PCS	S100B	RB	28.6±3.98 years	M	5 C+, 27 C–	Before competition, immediately postmatch and 36 hours postmatch	Moderate
Daley M, 2016[80]	PCS	Multiple metabolites	IH	Control: 12.9±1.0 years; concussed: 13.4±2.3 years	M	12 C+, 17 C– (age, sex and sport matched controls)	2.3±0.7 days postinjury	High
Hutchison MG, 2016[82]	PCS	Cortisol	FB, SCR, IH, LX, OT	21.0±2.5 years	M/F	26 C+, 26 C– (age, sex and sport matched controls)	Within 1 week, after symptom resolution and 1 week after return to play	Moderate
La Fountaine MF, 2016[84]	CS	PRL	Any	20±1 years	M	4 C+	Within 48 hours, 7 days and 14 days postinjury	High
Meier TB, 2016[41]	PCS	Tau	FB, SCR, OT	Control: 20.3±1.5 years; concussed: 20.1±1.4 years	M/F	40 C+, 46 C– (collegiate contact-sport controls)	1 day, 1 week and 1 month postinjury	High
Shahim P, 2016[79]	PCS	Tau	IH	P	M	28 C+	BL, 1 hour, 12 hours, 36 hours, 144 hours postinjury and the day the athlete returned to play	Moderate
Shahim P, 2016[81]	PCS	Tau, NF-L, GFAP, amyloid β, NG	IH	Control: median 25 years; concussed: median 31 years	M	16 C+, 15 C–	Median time from injury to examination was 4 months	Moderate

Definitions and coding for Table 3: Author indicates last name of first author. Year refers to year of publication.
Study type coded as follows: CS, clinical series; PCS, prospective cohort study.
Modality refers to specific fluid biomarker(s) used in the study: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor peptide; S100B, S100 calcium binding protein B; NSE, neuron specific enolase; MBG, marinobufagenin; PrPC, plasma soluble cellular prion protein; GFAP, glial fibrillary acidic protein; VILIP-1, Visinin-like protein-1; SNTF, calpain-derived αII-spectrin N-terminal fragment; QUIN, quinolinic acid; 3HK, 3-hydroxykynurenine; KYNA, kynurenic acid; PRL, prolactin; NF-L, neurofilament light; NG, neurogranin.
Sports coded as follows: BX, boxing; FB, football; FH, field hockey; IH, ice hockey; LX, LaCrosse; OT, other; RB, rugby; SCR, soccer; WR, wrestling.
Age/Level coded as follows: Col, college; HS, high school; P, professional; O, other; Y, youth.F/M indicates gender: F, female; M, male; list both if it applies.Misc: BL, baseline.
Risk of bias: overall risk of bias rated as low, moderate, high or unclear, based on modified QUADAS-2 critical appraisal tool (see online supplementary appendix 2).

Table 4 Data extraction tool for studies using genetic testing

	Study design		Participants					Review of evidence
First author, year	Study type	Modality	Sport	Age/level (mean ± SD, range)	Gender (M/F)	n (control description)	Time from injury to examination	Risk of bias
McDevitt J, 2015[87]	PCS	VNTR/GRIN2A	Any	19.5±6.0 years	M/F	87 C+	Recovery followed prospectively; ≤60 days postinjury	High
Gill J, 2016[85]	PCS	RNA	Any	Control: 18.5±0.4 years; concussed: 19.4±1.5 years	M/F	15 C+, 16 C–	BL, within 6 hours and 7 days postinjury	Moderate
Madura SA, 2016[90]	PCS	SLC17A7	Any	20.0±6.3 years	M/F	40 C+	Recovery followed prospectively; ≤20 days postinjury	High
Merchant-Borna K, 2016[86]	PCS	mRNA	FB, IH, SCR, LX	Control: 18.5±0.4 years; concussed: 19.4±1.5 years	M/F	16 C+, 16 C– teammate controls (253 C– at BL including C+ athletes)	BL, within 6 hours, and 7 days postinjury	Moderate
Merritt VC, 2016[89]	PCS	APOE	Any	19.3±1.5 years	M/F	45 C+, 43 C–	10.0±14.3 days postinjury	Moderate
Merritt VC, 2016[88]	CS	APOE	Any	Positive ϵ4 allele group 19.9±1.4 years; negative ϵ4 allele group 20±1.6 years	M/F	42 C+	9.8±14.6 days postinjury (range of 0–72 days)	Moderate

Definitions and coding for Table 4: Author indicates last name of first author. Year refers to year of publication.
Study type coded as follows: CS, clinical series; PCS, prospective cohort study.
Modality refers to specific genetic marker(s) studied: VNTR, variable number tandem repeats; GRIN2A, N-methyl-D-aspartate receptor 2A; APOE, Apolipoprotein e; SLC17A7, Solute Carrier Family 17 Member 7.
Sports coded as follows: BX, boxing; FB, football; FH, field hockey; IH, ice hockey; LX, LaCrosse; OT, other; RB, rugby; SCR, soccer; WR, wrestling.
Age/Level coded as follows: Col, college; HS, high school; O, other; P, professional; Y, youth.
F/M indicates gender: F, female; M, male; list both if it applies.
Misc: BL, baseline.
Risk of bias: overall risk of bias rated as low, moderate, high or unclear, based on modified QUADAS-2 critical appraisal tool (see online supplementary appendix 2).

A rating for the overall level of evidence was assigned for each search area (neuroimaging, biomarkers and genetics) based on a simple hierarchical 'level of evidence' grading system, modified from that established by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group (see table 5).[24] In cases of uncertainty, the full article was obtained and any disagreement resolved through discussion and consultation with a third reviewer. Finally, a qualitative synthesis of the overall level of evidence from each of the three searches was conducted by the subject matter experts and reported in each results section.

Table 5 Quality of evidence grades

Grade	Definition
High	High level of confidence in the strength of the existing findings demonstrating reliability, validity and clinical utility of the tool(s) for use in the assessment of SRC
Moderate	Moderate level of confidence in the strength of the existing findings demonstrating reliability, validity and clinical utility of the tool(s) for use in the assessment of SRC
Low	Low level of confidence in the strength of the existing findings demonstrating reliability, validity and clinical utility of the tool(s) for use in the assessment of SRC
Very low	Very Low level of confidence in the strength of the existing findings demonstrating reliability, validity and clinical utility of the tool(s) for use in the assessment of SRC

Quality of evidence is a continuum; any discrete categorisation involves some degree of arbitrariness. Nevertheless, advantages of simplicity, transparency and vividness outweigh these limitations.
SRC, sport-related concussion.

RESULTS

The electronic literature database search identified 3222 articles. After applying additional requirements and eliminating duplicate articles, a total of 98 qualified for further review (76 neuroimaging, 16 biomarkers and 6 genetic testing). Tables 2–4 provide a summary of key findings from studies in each domain (neuroimaging, biomarkers and genetic testing).

Neuroimaging studies

Seventy-six studies using neuroimaging and electrophysiological measures revealed significant effects of SRC by each of the modalities assessed in this review. These included diffusion tensor imaging (DTI) (n=18), task-based functional MRI (fMRI) (n=15), electroencephalogram (EEG)/quantitative-EEG (qEEG:n=16), magnetic resonance spectroscopy (MRS) (n=13), and resting-state fMRI (n=8), as well as fewer studies that used measures of cerebrovascular reactivity (CVR) (n=4), arterial spin labelling (n=5), transcranial magnetic stimulation (TMS) (n=3), susceptibility weighted imaging (n=2) and functional near-infrared spectroscopy (n=1). Although EEG and TMS were not explicitly referenced in our assigned review questions, the decision was made to include them in the neuroimaging section of the review based on published reports using these technologies in the study of SRC. The limited number of studies for any specific marker, the varying time frames, the lack of standardisation and the different analyses employed make the determination of consistent patterns difficult.

Nevertheless, some consistent patterns do emerge. With MRS there is a reduction of N-acetylaspartate (NAA; relative to creatine and/or choline) predominately in white matter,[25–32] with some evidence of acute reduction with subsequent recovery by

McCrea M, *et al*. *Br J Sports Med* 2017;**51**:919–929. doi:10.1136/bjsports-2016-097447

30 days postinjury.[30 32] Others, however, have reported decreased NAA levels more chronically.[25 33] Fewer studies have observed the effects of SRC on other metabolites,[27 31 33–35] although null results have also been reported.[36 37]

The majority of DTI work reports a decrease in mean diffusivity and/or an increase in fractional anisotropy in white matter within 6 months postinjury,[15 38–44] although opposite patterns or null results have been reported.[10 37 45 46] In addition, most observed a reduction in radial diffusivity,[38 39 42 43] whereas both increases and decreases in axial diffusivity have been described.[39 40 42 43]

The results from task-fMRI studies are more variable. The majority used a working memory paradigm leading to varying and seemingly contradictory findings, with reports of increased[47 48] and decreased activity in task-related networks (eg, dorsolateral prefrontal cortex).[11 49–51] Multiple studies, however, have reported additional activity outside of the core task regions following SRC in a variety of tasks.[11 49 50 52–54] Time since injury, task variables and symptom presentation are likely modifying factors. In addition, although most studies investigated working memory, the type and number of stimuli used (ie, low vs high working memory 'load') varied largely, which may explain apparent discordance in hypoactivation versus hyperactivation results reported.

Findings from the resting-state fMRI literature also vary, likely because methodologies differ. Nevertheless, the default mode network (DMN) is the most extensively studied network in the SRC literature. Results have varied across studies, however, as both increases and decreases in connectivity between DMN regions have been reported across and within studies.[46 55–57] Altered functional connectivity has also been observed relative to executive function, visual and motor networks.[55 58–60]

Several studies have demonstrated the effects of SRC on EEG/qEEG at rest or during different task conditions. Importantly, multiple studies assessed electrophysiological changes following injury relative to a preinjury baseline measure.[4 61–64] For example, Cao and Slobounov have reported differences in several EEG metrics postinjury relative to baseline.[61 62] Measures from qEEG have also been shown to be altered at 8 days post-SRC relative to baseline,[4] and have been associated with concussion severity, underlining the potential of electrophysiological measurements in the assessment of SRC.[65]

Consistent findings across the other modalities are difficult to assess due to the limited number of studies. However, four of five studies that investigated cerebral blood flow following SRC reported reductions at the acute and subacute phases (days to weeks),[14 37 66] and even at more chronic time points (~5 months).[25] An additional study reported no differences in resting cerebral blood flow,[57] although it did report an increase in CVR, consistent with others that showed impaired CVR.[67–69]

The majority of neuroimaging studies, although of high quality and informative, had at least a moderate risk of bias based on the scoring criteria outlined in the modified QUADAS-2 tool. Most common was the lack of generalisability due to the inclusion of limited age ranges, male athletes focus and/or limited sample sizes. Additional factors included a lack of appropriate control groups, lack of preinjury enrolment and potential for measurement bias due to limited information regarding the definition/diagnosis of mTBI/SRC. Also, publication bias that limits reporting null results should be acknowledged, although this issue is not unique to the current literature.

Given the above, it is our opinion that the level of evidence for the role of these neuroimaging and electrophysiological measures in the *clinical assessment* of SRC is low (see table 5) because the most studies reviewed were not designed to specifically assess clinical potential. Rather, they aimed to assess the effects of SRC using that marker. Therefore, for the purposes of this review, we make a distinction between the level of evidence for the utilisation of these markers for clinical assessment of SRC and their use to characterise the pathophysiology involved. It is our opinion that there is a significant role for neuroimaging and electrophysiological measures in characterising the pathophysiology of SRC.

Fluid biomarker studies

Sixteen papers met our inclusion/exclusion criteria relevant to diagnosis or prognosis following sport concussion using fluid biomarkers (see table 3). Fourteen papers analysed blood (plasma or serum) biomarkers, one paper analysed salivary cortisol, and one paper analysed CSF. Eleven papers found significant alterations in one or more of the following blood biomarkers that could potentially aid in the diagnosis of SRC: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor peptide (AMPAR),[70] S100 calcium binding protein B (s100B),[71–74] total tau,[72] marinobufagenin,[75] plasma soluble cellular prion protein,[76] glial fibrillary acidic protein,[76] neuron-specific enolase (NSE),[77] calpain-derived αII-spectrin N-terminal fragment (SNTF),[78] tau-C[79] and metabolomics profiling.[80] In contrast, NSE,[72] visinin-like protein-1,[74] total tau,[41 74 81] tau-A[79] and salivary cortisol[82] did not distinguish concussed athletes from non-concussed athletes. Several serum biomarkers such as SNTF,[78] quinolinic acid,[83] prolactin[84] and tau-A[79] showed early evidence in predicting outcomes following sport concussion. Finally, decreased levels of amyloid-beta-42 and increased neurofilament light in CSF were observed in athletes with postconcussion syndrome, although these results were largely driven by athletes with postconcussion syndrome duration of more than 1 year.[81]

Overall risk of bias rating for the fluid biomarker papers ranged from moderate to high. High risk of bias occurred most commonly due to limited external validity and poor generalisability in terms of gender (males only), age (collegiate athletes) and sport (most often football or ice hockey). Other factors contributing to moderate to high risk included small sample sizes, no control subjects and lack of preseason assessment. Based on our review of the existing literature, the overall level of evidence for use of fluid biomarkers in the *clinical assessment* of SRC is considered low (see table 5). Early but limited evidence does indicate, however, that fluid biomarkers may inform our scientific understanding of the underlying pathophysiology of concussion in humans.

Genetic testing studies

Outcome after SRC is variable and unpredictable, suggesting that factors other than injury severity, such as host genotype, are important modulators. Emerging literature on genetic predictors of TBI highlights their relevance,[13] and suggests four broad contexts in which genetic variation could modulate outcome: (1) modulation of the impact of a given neurotrauma 'dose' in terms of injury extent, (2) modulation of repair mechanisms, thus impacting trajectory of recovery and ultimate functional outcome, (3) modulation of preinjury traits (eg, resilience) or cognition (cognitive reserve), and (4) interactions between genetic vulnerabilities to neurobehavioural disorders and neurotrauma (ie, role of comorbidities).

Our search strategy identified six papers specifically addressing genetic factors in SRC. Of these, two (from the same group) studied gene expression acutely (within 6 hours) and subacutely (within 7 days) after concussion in essentially the same cohort of collegiate athletes.[85 86] Comparison of preseason baseline and postinjury samples in this cohort of college athletes showed differential expression of genes driving immune and inflammatory pathways acutely, and hypothalamic–adrenal–pituitary axis function subacutely.

The other four papers tested hypotheses related to specific candidate genes. McDevitt *et al* (2015)[87] studied the role of variable number tandem repeat (VNTR) alleles in the promoter region of GRIN2A (a gene coding an NMDA glutamate receptor subunit) in a cohort of 87 concussed athletes. Recovery times over 60 days were associated with the long variant of the allele. Two studies from Merritt and colleagues[88 89] found an association of the APOEe4 allele with total symptom score, cognitive and physical symptoms, and the presence and severity of headache in a cohort of concussed collegiate athletes assessed a mean of 10 days after injury. Another study in a cohort of 40 concussed collegiate athletes examined the rs74174284 polymorphism in the promoter region of the SLC17A7 gene, and found that the C allele was associated with prolonged recovery times and poorer motor performance.[90]

Overall, the risk of bias in reviewed studies was moderate to high (related to small sample size, inadequate representation across age/gender/sport, poorly defined diagnostic methods for concussion, referral bias and failure to include non-concussed teammates exposed to repetitive head impacts as controls). The overall level of evidence for clinical application was determined as low (see table 5), prohibiting endorsement of genetic testing for clinical evaluation or management of SRC. However, the available studies provide 'proof of concept' that genetic assessment might identify those at risk for poor outcomes from SRC, even before injury. Although genetic assessment cannot yet be endorsed as a clinical tool in SRC management, it certainly warrants future research.

DISCUSSION

Over the past 20 years, there has been significant progress in our understanding of the underlying neurobiology and pathophysiology of mTBI and concussion from both basic animal models and human studies. Collectively, the fact that nearly 100 studies included in our systematic review have employed advanced technologies specifically in the study of SRC over the past 15 years is a clear indication of how research in this arena has progressed. That said, the current state of this work is limited by several factors, including the relatively small number of studies investigating each modality, small sample sizes across studies, varied study design, outcome measures and analytic methods, and lack of consistency in the timing of postinjury data collection points, and risk of bias due to very limited generalisability across studies.

The collective body included in our systematic review was considered to have at least moderate risk of bias based on our assessment. *The risk of bias rating was clearly affected more by limited generalisability than by any inherent or created bias in the traditional sense associated with investigator conflicts, research design, outside influence, etc*. Generalisability was limited largely by the size and scope of the study sample (eg, restricted to single gender or sport) in several studies. This will be an important consideration for future research efforts to overcome.

Ultimately, determining the utility of these advanced technologies likely divides into two parallel discussions: (1) their use as research tools to study changes in brain structure and function associated with SRC, and (2) their clinical application as diagnostic and prognostic markers of injury and recovery to assist in the assessment and management of athletes with SRC, over and above our current clinical tools. In terms of their current readiness for *clinical application*, our systematic review rated the level of evidence as low for advanced neuroimaging, low for fluid biomarkers and low for genetic testing (see table 5). At the same time, however, our systematic review generally supports the utility of advanced neuroimaging, fluid and genetic biomarkers in studies aimed at identifying the neurobiological effects of concussion and the natural history of neurobiological recovery after injury.

Our rating of the neuroimaging evidence is consistent with a recently published position statement from the Radiologic Society for North America on the use of advanced neuroimaging modalities in the assessment of TBI. Advanced neuroimaging is sure to play a critical role in the future study of SRC. Similarly, the use of fluid biomarkers has advanced our understanding of the pathophysiology of SRC, but the validation of these markers is in the preliminary stages. Clinically, blood biomarkers require hours of analysis and access to a basic science laboratory, which is not currently practical for assessing acute SRC in the competitive sports setting. Future studies with larger samples sizes, standardised protocols, and more stringent study designs that include baseline testing, appropriate controls, blinded analysis and real-life outcome measures, are needed before these markers are translated from 'bench to bedside'.

Further research is critical to determine whether the time course of neurobiological recovery is 'coupled' with clinical or subjective recovery (eg, resolutions of signs, symptoms and functional impairments), or the extent to which the tail of neurobiological recovery extends beyond the observed endpoint of clinical recovery. In a research setting, this work is a critical next step towards understanding the pathophysiology of concussion in humans. From a clinical perspective, discoveries along these lines also have translational significance to determining when athletes achieve full recovery and are fit to safely return to activity without elevated risk or vulnerability to additional injury. Further, the novel technologies may enable researchers to better determine the effects of repetitive head impact exposure on brain structure and function, even in the absence of frank concussion.

It should be acknowledged that genetic testing is not intended for use in the diagnosis of concussion, but has importance in determining the factors that influence risk of injury and recovery after SRC. Data from genetic studies may provide intriguing insights about the host response to concussion, although the absence of data on how such differential gene expression affects outcome limits inferences about whether these changes constitute a contributory disease mechanism or a reparative host response. There is a clear need for large-scale research efforts to determine the role that genetics plays in the broader space of TBI and with specific relevance to athletes with SRC.

Given the complex pathophysiology of concussion, it is considered unlikely that a singular diagnostic and prognostic biomarker solution will prevail. Rather, an integrated combination of specific imaging, fluid and genetic biomarkers is predicted to have the greatest utility to clinical care. Ultimately, research on neurobiological and genetic aspects of SRC is predicted to have major translational significance to evidence-based approaches to clinical management of athletes with SRC, much like applied clinical research has had over the past 20 years.

RECOMMENDATIONS FOR FUTURE RESEARCH DIRECTIONS

We offer the following recommendations in order to further accelerate the field's understanding of the pathophysiology of SRC and to determine the potential of these advanced technologies for the clinical assessment of SRC:

1. Enrolment of larger sample sizes with greater representation across sport, age and sex, particularly studies involving youth and female athletes.
2. Preinjury enrolment of athletes to allow truly prospective recruitment of consecutive injuries. Although often impractical for neuroimaging, collecting biomarkers at preinjury would represent an ideal study design.
3. Studies driven by a priori hypotheses based on current evidence on neuropathophysiology of concussion from preclinical models and non-sport head injury. Exploratory (hypothesis-generating) research may also lead to important breakthroughs.
4. Careful consideration regarding the control groups used (eg, controlling for head impact exposure vs concussive injury) in order to advance our understanding of the effects of both concussion and repetitive head impact exposure (without concussion) on brain structure and function.
5. Adopt standard injury criteria, time frames of assessment and multidimensional measures of outcome and recovery, as well as metrics and processing strategies within modalities/metrics to allow comparison across studies (eg, National Institute of Neurological Disorders and Stroke TBI Common Data Elements, Canadian Pediatric mTBI Common Data Elements).
6. Simultaneous assessment of multiple biomarkers to determine the additive value of each marker in the clinical assessment of SRC.
7. Rather than simply showing associations between measurements and diagnosis or outcome, it is important to demonstrate additional benefit of novel biomarkers over current approaches.
8. Clinical utility is more likely to derive from biomarker combinations rather than individual biomarkers; we recommend the exploration of biomarker panels, both within and across techniques.

Several limitations of our systematic search and review warrant consideration. First, we recognise that the scope of our assigned systematic review was purposefully broad in order to inform the 5th International Consensus Conference on Concussion in Sport, but still rendered a relatively small number of qualifying studies, particularly with respect to fluid biomarkers and genetics. In addition to the aforementioned methodological limitations that impact the quality of evidence from reviewed studies, we also acknowledge the potential for publication bias (eg, public reporting of positive findings only) affecting our results of the systematic review. Further, articles included for review were limited to those published in English language, raising the prospect that studies published in other languages are not represented here.

CONCLUSION

Our results indicate that advanced neuroimaging, fluid biomarkers and genetic testing show significant promise as research tools in the study of SRC, but require considerable further research to determine their ultimate utility in a clinical setting. Future research efforts should address current gaps to help guide and accelerate clinical translation.

What are the findings?

- Over the past two decades, there has been a major expansion of research on the neurobiology of SRC, marked by the increase in number of studies that have employed advanced neuroimaging and fluid biomarkers to measure the acute effects of SRC on brain structure and function.
- These technologies show significant promise as research tools, but require considerable further research to determine their ultimate clinical utility.
- Future research efforts should address current gaps that limit clinical translation, including greater consistency across the most advanced technology platforms, larger and more representative study samples (across age, gender, sport, etc), and more rigorous analytic methods across studies.

How might it impact on clinical practice in the future?

- Ultimately, this line of research on neurobiological and genetic aspects of SRC is predicted to have major translational significance to evidence-based approaches to clinical management of athletes with SRC, much like applied clinical research has had over the past 20 years.

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